

Dept Genetics
Univ of Wis.
(Madison, Wis.)

March 15. 1950.

Dr. H. J. Muller,
Dept. Zoology,
Indiana University,
Bloomington, Indiana.

Dear Dr. Muller:

I am seeking your counsel on an issue that is somewhat related to "mutational prophylaxis", and to which, therefore, I suppose you have given some thought.

Lately, we have been studying the mechanism of radiation killing of bacteria, by examining the effects of X-ray and UV on heterozygous diploid *E. coli*. It may not surprise you that recessive lethals do not play a detectable role in killing, but that there is a very striking degree of "haploidization" of the treated diploid cells, which I assume to reflect grosser chromosome damage and loss.

I next thought that this might be a useful method for classifying bactericidal compounds and agents into those with predominantly "nuclear", and predominantly "cellular" modes of killing. Nitrogen mustard, as expected, gave the same results as radiations. However, we were surprised to find that quite a considerable number of other organic reagents gave comparable results too, including: formaldehyde, dimethyl sulfate, acetic anhydride, and hydrogen peroxide. Killing by heat, basic dyes, iodoacetamide or iodine, urethane, and some others, had no detectable genetic correlate.

These results raise a number of questions, some of first theoretical interest. In view of the homologies, I think it is likely that radiogenetic effects are mediated by reactive compounds; free radicals, or ions which share the capacity to bring about substitution reactions, like those mediated by alkyl peroxides, cyclic ethan ammonium, formal, alkylating anhydrides, etc. The results do not bear on the problem of the immediacy of the effects on genes. But aside from this important theoretical question, I am led to wonder whether the potential mutagenic effects [speaking very broadly] of such a wide variety of organic reagents does not create a hazard broader even than those of ionizing radiations. Clearly, we do not know whether such agents are likely to induce mutations in mammals, considering problems of penetration, but it seems to me that this ignorance is potentially dangerous, for the same reason that personal ignorance of X-ray effects is dangerous to the species.

I wonder whether this whole problem should not be brought before some such body as the National Research Council. Ordinarily, I would not be very enthusiastic for programmatic research, but it is obvious that any undertaking to investigate mutagenic effects of industrial chemicals in mammals would have to be organized on a large scale, and receive very broad support, presumably from the Public Health Service or some other governmental agency. I do not know of any existing institution that would be capable of absorbing such a program. But I think that you will agree that no study of the toxicology of industrial compounds would be complete if it left unrelieved any suspicion of potential mutagenic effects.

My own experience with such matters is so limited that I feel that any comments you might make would be very valuable. Perhaps the problem is exaggerated, but I have the feeling that, in our ignorance, chemical mutagenesis poses a problem of the same magnitude as the indiscriminate use of radiations. On the other hand, it would be unfortunate if these notions were improperly publicised -- I should not like to see many repetitions of the "Elastophthoric lead poisoning", which appeared in ~~the~~ Journal of Heredity a year or so ago.

Yours sincerely,

Joshua Lederberg